☐ 1: Proc Natl Acad Sci U S A 1993 Nov 1;90(21):10154-8

Multiple integrins mediate cell attachment to cytotactin/tenascin.

Prieto AL, Edelman GM, Crossin KL.

Scripps Research Institute, Department of Neurobiology, La Jolla, CA 92037.

To identify potential cell surface receptors for chicken cytotactin (CT), we have characterized the ability of recombinant fusion proteins spanning the proximal fibronectin (FN) type III repeats of the molecule to support attachment of glioma and carcinoma cell lines. The third FN type III repeat, which contains the RGD tripeptide, supported cell attachment and cell spreading; however, mutation of RGD to RAD did not result in significant loss of either activity. In addition, the same repeat of mouse CT, which contains a natural mutant, RVD, also supported cell attachment and spreading, although at a lower level; both activities were increased by mutation of the RVD sequence to RGD. Studies utilizing RGD-containing peptides and well-characterized antibodies to integrins indicated that cell attachment to the third FN type III repeat was mediated by at least two different integrin receptors of the alpha v subtype. Additional cellular receptors may also be involved in cell attachment to CT. For example, an antibody to the beta 1 subfamily of integrins partially inhibited binding of cells to intact CT but did not inhibit cell binding to the third FN type III repeat. These findings suggest that the RGD site in CT is able to mediate cell attachment to integrins and thus is not a cryptic adhesion site. They also open the possibility that the functions of CT in processes such as counteradhesion, cell migration, cell proliferation, and cell differentiation may be mediated in part by interaction with multiple integrins.

PMID: 7694284 [PubMed - indexed for MEDLINE]

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☐ 1: In Vitro Cell Dev Biol 1985 Jan;21(1):73-8

Effects of fibronectin-related peptides on cell spreading.

Silnutzer JE, Barnes DW.

Four synthetic peptides related in amino acid sequence to the area of the fibronectin molecule thought to be involved in cell binding were tested for the ability to inhibit cell spreading promoted by several different attachment factors. Effects of the peptides were assayed on a number of cell types. For all cell types tested, peptides effective at inhibiting fibronectin-promoted cell spreading were found also to inhibit cell spreading promoted by human serum spreading factor (SF). These peptides were also capable of inhibiting to a lesser extent cell spreading promoted by other attachment factors, although this phenomenon was dependent on the cell type examined.

PMID: 4086426 [PubMed - indexed for MEDLINE]

1: J Cell Biol 1987 Jan;104(1):131-9

Platelet thrombospondin mediates attachment and spreading of human melanoma cells.

Roberts DD, Sherwood JA, Ginsburg V.

Human platelet thrombospondin adsorbed on plastic promotes attachment and spreading of human G361 melanoma cells. Attachment is rapid, and spreading is maximal by 90 min with 60-90% of the attached cells spread. In contrast, thrombospondin promotes attachment but not spreading of human C32 melanoma cells, which attach and spread only on laminin substrates. The specificity of these interactions and the regions of the thrombospondin molecule involved in attachment and spreading were examined using proteolytic fragments of thrombospondin and by inhibition studies. The sulfated fucan, fucoidan, and monoclonal antibody A2.5, which is directed against the heparin-binding domain of thrombospondin, selectively inhibit spreading but only weakly inhibit attachment. Monoclonal antibodies against some other domains of thrombospondin, however, are potent inhibitors of attachment. The amino-terminal heparin-binding domain of thrombospondin does not promote attachment. Large fragments lacking the heparin-binding domain support attachment but not spreading of G361 cells. Attachment activity is lost following removal of the 18-kD carboxyl-terminal domain. These results suggest that at least two melanoma ligands are involved in cell attachment and spreading on thrombospondin. The carboxyl-terminal region and perhaps other regions of the molecule bind to receptor(s) on the melanoma surface that promote initial attachment but not cell spreading. Interaction of the heparin-binding domain with sulfated glycoconjugates on melanoma surface proteoglycans and/or sulfated glycolipids mediates spreading. Monoclonal antibodies A2.5 and C6.7 also reverse spreading of G361 cells growing on glass culture substrates, suggesting that binding to thrombospondin mediates attachment of these melanoma cells in culture.

PMID: 3793757 [PubMed - indexed for MEDLINE]

☐ 1: J Biol Chem 1992 Sep 25;267(27):19349-55

Heparin-binding peptides from the type I repeats of thrombospondin. Structural requirements for heparin binding and promotion of melanoma cell adhesion and chemotaxis.

Guo NH, Krutzsch HC, Negre E, Zabrenetzky VS, Roberts DD.

Laboratory of Pathology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892.

Synthetic peptides derived from the type I repeats of human platelet thrombospondin containing a consensus sequence Trp-Ser-Xaa-Trp bind to heparin, promote cell adhesion, and inhibit heparin-dependent interactions of melanoma cells with extracellular matrix components (Guo, N. H., Krutzsch, H. C., Negre, E., Vogel, T., Blake, D. A., and Roberts, D. D. (1992) Proc. Natl. Acad. Sci. U.S.A. 89, 3040-3044). In the present study, we further examined the structural requirements for activity of these peptides. The minimal active sequence for heparin or sulfatide binding based on inhibition studies is Trp-Ser-Pro-Trp, although an octapeptide is required for optimal activity. The 2 Trp residues and the Ser residue are essential. Peptides with more than 2 residues between the Trp residues are inactive. The Pro residue is essential for activity of the pentapeptide Trp-Ser-Pro-Trp-Ser, but some larger peptides with substitutions for the Pro residue are active. For direct high affinity binding to heparin, both the consensus sequence and a flanking sequence of basic amino acids are essential. Peptides containing the consensus sequence promote cell adhesion and act cooperatively with the adjacent basic amino acid sequence to promote cell spreading. Chemical modification of the Trp residues in the peptides with amino-terminal basic amino acids abolished both cell adhesion and heparin-binding. Peptides containing the consensus sequence and basic amino acids are chemotactic for A2058 human melanoma cells. The functional importance of this novel heparin and sulfatide-binding motif is suggested by its conservation in other members of the thrombospondin gene family, complement components, and in many members of the cytokine receptor and transforming growth factor beta superfamilies.

PMID: 1527055 [PubMed - indexed for MEDLINE]

☐ 1: Biochem Biophys Res Commun 1993 Oct 29;196(2):984-9

Expression of receptors for advanced glycosylation end products on renal cell carcinoma cells in vitro.

Miki S, Kasayama S, Miki Y, Nakamura Y, Yamamoto M, Sato B, Kishimoto T.

Nissei Hospital, Osaka, Japan.

Proteins that have been modified by long-term expose to glucose accumulate advanced glycosylation end products (AGEs) as a function of protein age. In these studies, we have examined the interaction of AGE-protein with renal cell carcinoma cells (RCC) in vitro, using AGE-modified bovine serum albumin (AGE-BSA) as a probe. AGE-BSA showed tendency to induce in vitro cell growth of RCC cells and promoted the production of interleukin-6 (IL-6), an in vitro autocrine growth factor. Reverse transcriptase-polymerase chain reaction analysis revealed that RCC cells used here express mRNA for a receptor for AGEs (RAGE). These results suggested that AGEs taken up through RAGE on RCC cells might play a role in promoting the growth of RCC cells.

PMID: 8240377 [PubMed - indexed for MEDLINE]

1: J Biochem (Tokyo) 1996 Aug;120(2):445-51

Novel peptide ligands for integrin alpha 6 beta 1 selected from a phage display library.

Murayama O, Nishida H, Sekiguchi K.

Research Institute, Osaka Medical Center for Maternal and Child Health.

Integrin alpha 6 beta 1 is a major adhesion receptor for the basement membrane, specifically binding to laminin-1. To identify the peptide sequences recognized by alpha 6 beta 1, we screened a 15-mer phage display library by panning with alpha 6 beta 1 purified from human placenta. DNA sequencing of 73 randomly picked phage revealed that three clones were dominantly enriched after repeated panning with alpha 6 beta 1. None of the peptide sequences displayed on these phage showed significant homology to laminin-1. A synthetic peptide modeled after the sequence displayed by one of these phage, designated P3, was found to strongly inhibit the binding of laminin-1 to alpha 6 beta 1. This inhibitory effect of the P3 peptide seems to be specific for alpha 6 beta 1, since it did not affect the binding of fibronectin to integrin alpha 5 beta 1. A synthetic peptide with a scrambled P3 amino acid sequence barely inhibited the binding of laminin-1 to alpha 6 beta 1. When coated on a substratum after conjugation with bovine serum albumin, the P3 peptide was capable of promoting cell spreading in an alpha 6 beta 1-dependent manner, although the peptide with the scrambled sequence showed activity similar to that of a control peptide. These results taken together indicate that the P3 peptide is a novel ligand for integrin alpha 6 beta 1 with potent cell spreading activity.

PMID: 8889832 [PubMed - indexed for MEDLINE]

1: Cancer Res 1989 Feb 1;49(3):681-6

Relationship between extracellular matrix interactions and degree of differentiation in human colon carcinoma cell lines.

Daneker GW Jr, Piazza AJ, Steele GD Jr, Mercurio AM.

Laboratory of Cancer Biology, New England Deaconess Hospital, Boston, MA 02115.

Human colon carcinoma cell lines that vary in their degree of differentiation were examined for their ability to interact with extracellular matrix components. For this purpose, established cell lines were classified on the basis of several criteria that relate to degree of differentiation. These criteria include histology of the original tumor, histology of xenografts, in vitro morphology, and carcinoembryonic antigen expression. On this basis, the cell lines used were either moderately well or poorly differentiated. The poorly differentiated cell lines adhered to surfaces coated with laminin or reconstituted basement membrane extract (Matrigel) to a significantly greater extent than the moderately well differentiated lines with the exception of one moderately well differentiated line that was derived from a highly aggressive signet ring cell carcinoma. In addition, the poorly differentiated cell lines exhibited considerable spreading on laminin and Matrigel after adherence that was not evident for the moderately well differentiated lines. The adherence of these cell lines on fibronectin-coated surfaces did not correlate as well with differentiation although, in general, poorly differentiated cell lines adhered better than moderately well differentiated lines. None of the cells that adhered to fibronectin exhibited the extensive spreading seen on laminin. The specificity of tumor cell interactions with extracellular matrix glycoproteins was examined using synthetic peptides which correspond to sequences within these proteins that are recognized by cell surface receptors. The pentapeptide YIGSR-NH2 significantly inhibited the adherence and spreading of the tumor cell lines on laminin, but not on fibronectin. The peptide RGDS, however, did not inhibit tumor cell interactions with laminin although it did inhibit their interactions with fibronectin. Thus, the interactions of colon carcinoma cells with laminin and fibronectin are probably mediated by separate receptors. Taken together, the data demonstrate that cells derived from colon carcinomas exhibit considerable variation in their ability to interact with extracellular matrix components, and that this variability is related to the degree of

differentiation of original tumor.

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